
High-throughput characterization of the role of non-B DNA motifs on promoter function.

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Public Summary:

Georgakopoulos-Soares et al. performed computational analyses of germline mutations and identified increased mutability at non-B DNA motifs. The contribution of non-B DNA motifs on gene expression was investigated using massively parallel reporter assays, identifying Z-DNA as a positive regulator of gene expression and finding that the orientation of G-quadruplexes influences promoter activity.

Scientific Abstract:

Alternative DNA conformations, termed non-B DNA structures, can affect transcription, but the underlying mechanisms and their functional impact have not been systematically characterized. Here, we used computational genomic analyses coupled with massively parallel reporter assays (MPRAs) to show that certain non-B DNA structures have a substantial effect on gene expression. Genomic analyses found that non-B DNA structures at promoters harbor an excess of germline variants. Analysis of multiple MPRAs, including a promoter library specifically designed to perturb non-B DNA structures, functionally validated that Z-DNA can significantly affect promoter activity. We also observed that biophysical properties of non-B DNA motifs, such as the length of Z-DNA motifs and the orientation of G-quadruplex structures relative to transcriptional direction, have a significant effect on promoter activity. Combined, their higher mutation rate and functional effect on transcription implicate a subset of non-B DNA motifs as major drivers of human gene-expression-associated phenotypes.

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